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(54) Pharmaceutically stable compound consisting of timolol, dorzolamide and brimonidine

(57) The present invention is related to ophthalmic formulations for the treatment of ocular ailments. More specifically, it is related to the pharmaceutical industry in the production of ophthalmic medication for the treatment of ocular hypertension. The advantage of the present invention over other state of the art treatments is that it achieves a composition of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate with excellent properties of stability; it does not give rise to chemical reactions which produce modifications in the active molecules; with no antagonistic effects among the components. The present invention consists of a stable pharmaceutical composition for the treatment of ocular hypertension characterized by consisting of the following excipients: Polyoxyl 40 Stearate, Sodium Borate crystals, Sodium Chloride, Mannitol and Benzalkonium chloride.

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Description

FIELD OF THE INVENTION

[0001] The present invention is related to ophthalmic formulations for the treatment of ocular ailments. More specifically, it refers to a formulation in a Timolol Maleate, Dorzolamide Hydrochloride and Brimonidine Tartrate based solution, which contains a combination of a tonifying agent, a buffer agent and a solubilizing agent and a preservative agent and which may be characterized by having excellent stability properties. More specifically, the present invention is related to the pharmaceutical industry and the production of ophthalmic medicine for the treatment of ocular hypertension.

BACKGROUND OF THE INVENTION

[0002] The combination of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate has proven to have significant advantages over state of the art ocular hypertension agents.

[0003] It is well known that pharmaceutical compositions in general are made up of excipients with diverse functions.

[0004] In the case of ophthalmic medications, for external use on the eye, the products are generally liquid solutions.

[0005] In order to obtain a stable formula, it is important to consider various excipients which are necessary to obtain chemical stability, preventing the active ingredients which make up the excipient from degrading or reacting among themselves, such as a pH buffer, a preservative, an agent which regulates the osmolarity, a solubilizing agent, etc.

[0006] That is to say, the excipients are a combination of a tonifying agent, a buffering agent, a solubilizing agent and a preservative agent.

[0007] Notwithstanding this knowledge within the state of the art, pharmaceutical research and development are necessary in order to determine which specific excipients may be used in a product in combination with the three molecules in question.

[0008] Mannitol is widely used in pharmaceutical formulas and food. It is mainly used in pharmaceutical preparations as a diluent in tablets and in liquid solutions to adjust the osmolarity.

[0009] Therapeutically Mannitol which is parenterally administered is used as an osmotic diuretic, as a diagnostic agent of kidney function, as well as being used to reduce intracranial pressure, in the treatment of cerebral edema and to reduce intraocular pressure.

[0010] Mannitol is present in almost all vegetables. It acts as a laxative if consumed in large amounts. Following an intravenous injection, Mannitol is not metabolized and is only absorbed slightly in the renal tract, thus about 80% of the dose is excreted in urine in the first 3 hours.

[0011] Polyoxyl 40 stearate is generally used as an emulsifier in oily/water type creams and lotions. Polyoxyl 40 stearate has been used as an emulsifying agent in intravenous infusions.

[0012] Although Polyoxyethylenes are mainly used as emulsifying agents in pharmaceutical formulas for external use, certain materials, specifically Polyoxyl 40 stearate, have also been used in intravenous injections and oral preparations.

[0013] Polyoxyethylenes stearates have been extensively tested for toxicity in animals and are widely used in pharmaceutical and cosmetic formulations.

[0014] They are generally classified as non-toxic and non-irritant materials.

[0015] The combination of Boric Acid and Sodium Borate possesses good buffering ability and is commonly used in ophthalmic preparations as pH buffers.

[0016] Sodium Chloride is widely used in a variety of parenteral and non-parenteral pharmaceutical formulations, where the principle purpose is to produce isotonic solutions. In ophthalmic formulations the main use is to regulate osmolarity.

[0017] Sodium Chloride is the most important salt found in the body; it regulates osmotic tension in the blood and tissues. Approximately 5 to 12 g of Sodium Chloride are consumed daily by an individual on a normal diet and the same amount is excreted in urine every day. As an excipient Sodium Chloride may be added as a non-toxic and non-irritant material.

[0018] Benzalkonium chloride is a component of quaternary ammonium which is used in pharmaceutical formulations as a preservative in similar applications to other cationic surfactant agents such as Cetrimide.

[0019] In ophthalmic formulations Benzalkonium chloride is one of the most widely used preservatives, used in concentrations of between 0.01 and 0.02 %.

[0020] Benzalkonium chloride is usually not irritating and is well tolerated in the concentrations normally used on the skin and mucose. However, Benzalkonium chloride has been associated with adverse effects in some ophthalmic formulations. Toxicity experiments on rabbits show that Benzalkonium chloride is damaging in concentrations above those which are normally used in formulations. However, the human eye seems to be less affected than the eye of a rabbit.

[0021] To date, there is no known ophthalmic formulation which specifically suggests the combination of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate for the treatment of ocular hypertension, and thus the present

invention has inventive merits of its own as will become evident through the following description.

OBJECTIVES OF THE INVENTION

[0022] One of the objectives of the invention is to achieve a composition of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate which is phisiochemically compatible and stable.

[0023] Another objective is to determine the qualitative composition of the excipients which achieve the previous objective.

[0024] Still another objective is to determine whether, in the combinations which achieve the first objective, chemical reactions occur which produce modifications in the active molecules.

[0025] Yet another objective of the present invention is to demonstrate that there is no antagonistic effect among the components.

[0026] All of the previous objectives will become apparent through the following description and the annexes.

BRIEF DESCRIPTION OF THE INVENTION

[0027] The present invention consists of a qualitative composition as well as a novel quantitative composition for the treatment of ocular hypertension containing a combination of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate, with excipients which allow for the co-existence of the three active principles with good stability.

[0028] Following multiple efforts of selection, it was determined that base composition of the excipients should contain at least the following components: Polyoxyl 40 stearate, Sodium Borate crystals, Sodium chloride and Benzalkonium chloride.

[0029] In one of the preferred incorporations, Mannitol is included in the composition of the previous base excipients.

[0030] In another of the preferred incorporations Hydroxypropyl-beta-cyclodextrines and sodium hyaluronate are added to the qualitative composition of base excipients.

[0031] In general, one of the aspects of the invention consists of a composition of Dorzolamide Hydrochloride, Timolol Maleate and Brimonidine Tartrate, with the following quantitative composition:

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Mannitol	0.0-0.50
Hydroxypropyl-beta-cyclodextrines	0.0-1.0
Sodium Hyaluronate	0.0-0.20
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0032] Based on the results of tests of excipient compatibility, the base was obtained for carrying out the following formulas which underwent accelerated stability during 3 months (40°C) in low density polyethylene jars.

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022

(continued)

Component	Amount (g)
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0033] There is a second formula with the following content:

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Mannitol	0.50
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0034] And finally a 3rd formula with the following content:

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Hydroxypropyl-beta-cyclodextrines	1.0
Sodium Hyaluronate	0.20
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0035] In order to better understand the invention, following is a detailed description of the present invention showing the results of various tests carried out with the chosen composition.

DETAILED DESCRIPTION OF THE INVENTION

[0036] Following is a detailed description of the two facets of the present invention:

[0037] Following multiple efforts to decide, the base compound of the excipients should include at least the following components: a solubilizing agent such as Polyoxyl 40 Stearate, an agent which helps to buffer the pH such as Sodium Borate crystals, a tonifying agent such as Sodium Chloride and an antimicrobial preservative such as Benzalkonium chloride.

[0038] In one of the preferred incorporations, another tonifying agent is added to the composition of the base compound,

that being Mannitol.

[0039] In another preferred incorporation Hydroxypropyl-beta-cyclodextrines and Sodium Hyaluronate are added to the qualitative composition of the base compounds.

[0040] Based on the results of compatibility tests of the excipients, the base needed to carry out the following formulas was found, these underwent accelerated stability during 3 months (40°) in low density polyethylene jars.

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0041] A second formula with the following content was obtained:

Component	Amount(g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Mannitol	0.50
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0042] And finally a third formula with the following content:

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Hydroxypropyl-beta-cyclodextrines	1.0
Sodium Hyaluronate	0.20
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

[0043] Tests were carried out on 5 people to determine the level of stinging. Following are the results:

1: NULL 2: SLIGHT 3: INTENSE					
	PERSON 1	**PERSON 2**	**PERSON 3**	**PERSON 4**	**PERSON 5**
Formula 1	3	3	3	3	3
Formula 2	2	2	2	2	2
Formula 3	2	2	2	2	2

[0044] Based on the preceding results, only formulae 2 and 3 underwent accelerated stability.

[0045] Following are the results of the tests for accelerated stability:

TIMOLOL MALEATE

[0046]

FORMULA	**INITIAL***	**1 MONTH**	**2 MONTHS**	**3 MONTHS**
2	100.0	101.01	99.89	102.73
3	100.0	99.59	101.20	103.72
*Results normalized at 100 %.				

BRIMONIDINE TARTRATE

[0047]

FORMULA	**INITIAL***	**1 MONTH**	**2 MONTHS**	**3 MONTHS**
2	100.0	96.25	98.23	103.31
3	100.0	110.00	96.80	102.14
*Results normalizaded at 100 %.				

DORZOLAMIDE HYDROCHLORIDE

[0048]

FORMULA	**INITIAL***	**1 MONTH**	**2 MONTHS**	**3 MONTHS**
2	100.0	101.79	103.64	104.69
3	100.0	124.0	99.11	104.82
*Results normalized at 100 %.				

[0049] Based on the results of stability, Formula F 2 was chosen due to its chemical stability and less stinging.

[0050] That is, in one of its preferred incorporations, the invention consists of:

Polyoxyl 40 Stearate	7.00 g
Sodium Borate crystals	0.56 g
Sodium Chloride	0.10 g
Benzalkonium chloride	0.02 g
Mannitol	0.50 g
Timolol Maleate	0.68 g
Brimonidine Tartrate	0.20 g

(continued)

Dorzolamide Hydrochloride	2.22 g
Water as a vehicle	100.0 mL

pH= 5.65.

[0051] Having established this as the optimum formula, certain tests were carried out to find the functional intervals of the components, finding the following intervals to be the most appropriate:

Polyoxyl 40 Stearate	6.15-8.00 g
Sodium Borate crystals	0.48-0.65 g
Sodium Chloride	0.09-0.12 g
Benzalkonium chloride	0.02-0.023 g
Mannitol	0.35-0.85 g
Timolol Maleate	0.68 g
Brimonidine Tartrate	0.20 g
Dorzolamide Hydrochloride	2.22 g
Water as a vehicle	100.0 mL

pH= 5.65.

[0052] The invention has been sufficiently described so that a person with average knowledge in the field may reproduce and obtain the results which we mention in the present invention. However, anyone skilled in the field of the art of the present invention may be able to make modifications not described in the present application and if in order to apply said modifications in a specific composition the material claimed in the following claims is required, said processes and solutions should be considered within the scope of the present invention.

Claims

1. A stable pharmaceutical composition for the treatment of ocular hypertension of the kind that consists of the active molecules Timolol Maleate, Brimonidine Tartrate and Dorzolamide Hydrochloride, **characterized by** fundamentally consisting of the following excipients: Polyoxyl 40 Stearate, Sodium Borate crystals, Sodium Chloride and Benzalkonium chloride.

2. A stable pharmaceutical composition for the treatment of ocular hypertension, as claimed in the preceding claim, **characterized by** also consisting of the excipient Mannitol.

3. A stable pharmaceutical composition for the treatment of ocular hypertension, as claimed in Claim 1, **characterized by** also consisting of the excipients: Hydroxypropyl-beta-cyclodextrines and Sodium Hyaluronate.

4. A stable pharmaceutical composition for the treatment of ocular hypertension, as claimed in Claims 1, 2 and 3, **characterized by** consisting of the following quantitative composition:

Component	Amount (g)
Polyoxyl 40 Stearate	5.0-7.0
Sodium Borate crystals	0.34-0.56
Sodium Chloride	0.10-0.18
Benzalkonium chloride	0.02-0.022
Mannitol	0.0-0.50
Hydroxypropyl-beta-cyclodextrines	0.0-1.0
Sodium Hyaluronate	0.0-0.20

(continued)

Component	Amount (g)
Timolol Maleate	0.68
Brimonidine Tartrate	0.20
Dorzolamide Hydrochloride	2.22
Water as a vehicle	100.0 ml

5. A stable pharmaceutical composition for the treatment of ocular hypertension, as claimed in Claim 2, **characterized by** consisting of a quantitative composition with the following content:

Polyoxyl 40 Stearate	6.15-8.00 g
Sodium Borate crystals	0.48-0.65 g
Sodium Chloride	0.09-0.12 g
Benzalkonium chloride	0.02-0.023 g
Mannitol	0.35-0.85 g
Timolol Maleate	0.68 g
Brimonidine Tartrate	0.20 g
Dorzolamide Hydrochloride	2.22 g
Water as a vehicle	100.0 mL

pH= 5.65.

6. A stable pharmaceutical composition for the treatment of ocular hypertension, as claimed in the preceding claim, **characterized by** consisting of a quantitative composition with the following content:

Polyoxyl 40 Stearate	7.00 g
Sodium Borate crystals	0.56 g
Sodium Chloride	0.10 g
Benzalkonium chloride	0.02 g
Mannitol	0.50 g
Timolol Maleate	0.68 g
Brimonidine Tartrate	0.20 g
Dorzolamide Hydrochloride	2.22 g
Water as a vehicle	100.0 mL

pH= 5.65.

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EUROPEAN SEARCH REPORT

Application Number
EP 08 38 0004

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A,P	WO 2007/121077 A (ALLERGAN INC [US]; GRAHAM RICHARD [US]; SCHIFFMAN RHETT M [US]; JOHNSO) 25 October 2007 (2007-10-25) * page 4, line 14 * * claims 1-14; examples 1,2 *	1-6	INV. A61K9/00 A61K31/535 A61K31/498 A61K31/382
A	US 2004/029771 A1 (RIGDON GREGORY C [US] ET AL) 12 February 2004 (2004-02-12) * claims 37-41,46 *	1-6	
A	US 2005/038103 A1 (SINGH AMARJIT [CA]) 17 February 2005 (2005-02-17) * claims 1-10; examples 1,2 *	1-6	
A	NOECKER R J ET AL: "CORNEAL AND CONJUCTIVAL CHANGES CAUSED BY COMMONLY USED GLAUCOMA MEDICATIONS" CORNEA, MASSON PUBL., NEW YORK, NY, US, vol. 23, no. 5, 1 July 2004 (2004-07-01), pages 490-496, XP009069206 ISSN: 0277-3740 * the whole document *	1-6	

TECHNICAL FIELDS SEARCHED (IPC)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	27 January 2009	Toulacis, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 08 38 0004

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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27-01-2009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007121077 A	25-10-2007	AU 2007238296 A1	25-10-2007
		EP 2007354 A1	31-12-2008
US 2004029771 A1	12-02-2004	NONE	
US 2005038103 A1	17-02-2005	CA 2470866 A1	13-02-2005

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82